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Memory: The Majestic Case of an Amnestic Trace

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Memories formed during infancy are forgotten in adulthood, a phenomenon called 'infantile amnesia'. New research suggests that these memories can be artificially recovered in adulthood, suggesting that they were never completely lost in the first place.

Think back to your earliest memory. How old were you? While some claim to recall memories from infancy, most adults cannot retrieve a memory for an event that occurred before the age of three [1,2]. This phenomenon is termed childhood or 'infantile' amnesia and has been observed in both humans and non-human species, including mice, one of the most important experimental lab animals. For example, an adult mouse can be fear conditioned when given a mild foot shock in a particular environment to form a contextual fear memory. Re-exposing the mouse to the environment elicits a defensive posture called freezing, which is characterized by a lack of movement or exploration. But if the mouse is fear conditioned as an infant (typically around 17 days after birth, or P17) and then is tested as an adult (typically around P60), the animal will not freeze, indicating that a type of amnesia has occurred. Neuroscientists have offered, and debated over, two potential explanations for such cases of infantile amnesia: a failure in encoding the memory because the neural machinery needed to store it is not yet fully developed in infants; or, a failure in retrieving the memory because it remains, somehow, inaccessible in the adult brain. In the library of memories, does infantile amnesia mean that the books were never stored away in the first place, or does it mean that the librarian no longer has direct access to a mnemonic novel? A new study by Guskjolen *et al.* [3] reported in this issue of *Current Biology* supports the latter hypothesis: in mice, infantile memories are accessible in adulthood when artificially reactivated from within the brain.

A motif of lost-and-found is emerging in memory research and the hippocampus — a key region that undergoes a critical period of development in childhood — has emerged as a leading candidate brain region involved in awakening dormant memories. Hippocampal networks remodel as they mature over time and enable memory storage and retrieval. A burgeoning body of literature supports the notion that infantile amnesia reflects a progressive switch in hippocampal functioning such that the adult hippocampus fails to facilitate the retrieval of a memory formed in infancy. For example, Travaglia *et. al.* [4] suggested that childhood memories are latent and can be effectively retrieved in adulthood if subjects are given the necessary environmental cues for retrieval. The observed infantile amnesia closely corresponded to critical periods of neurodevelopment, relied on plasticity-related proteins, and could be reversed when these proteins were upregulated in the hippocampus, demonstrating again that the memory had not disappeared but was dormant. In the developing brain, the librarian leaves when a shift is over.

Even when produced in adulthood, certain types of amnesia have been shown to be a failure of retrieving a once-lost hippocampus-mediated memory. Ryan *et al.* [5] induced amnesia in adult rodents and then successfully forced the retrieval of a memory by optogenetically stimulating hippocampus cells that were active during memory formation. Their finding was context-specific and relied on the integrity of both the hippocampus and structural connectivity between subsets of cells across hippocampus sub-regions, thus providing a conjunctive neural correlate of a memory trace that survives amnesia. Once again, despite the librarian's absence, it is possible to break into the adult brain and illuminate a hidden mnemonic novel.

In the new study, Guskjolen *et al.* [3] tested whether a fear memory formed during infancy could be successfully retrieved in adulthood via optogenetic stimulation of discrete sets of hippocampus cells. Using a strategy based on activity-dependent and inducible transgene expression [6], the authors first tagged hippocampal cells that were active during fear conditioning with the light-sensitive protein channelrhodopsin-2 (ChR2). These cells were then optogenetically reactivated across different retention delays, which remarkably led to a recovery of the memories formed in infancy up to 90 days after training, suggesting that the infantile amnesia typically observed is a failure in retrieving a memory (Figure 1). As a crucial control, animals that received stimulation of neurons that were tagged in their home cage or in a distinct context did not exhibit freezing, indicating that the observed memory recovery is specific to the reactivation of the cells active specifically during fear conditioning — an extraordinary demonstration of directly activating a context-specific memory thought to have been erased over time.

To measure the neural correlates of light-induced memory retrieval, Guskjolen *et al.* [3] then surveyed a variety of downstream brain regions and demonstrated that the recovery of a memory correlated with the reinstatement of hippocampal and cortical encoding patterns of activity. They first tagged cells in a brain-wide manner that were active during fear conditioning. After optogenetically stimulating hippocampus cells processing the original fear memory, the authors went on to quantify downstream neuronal populations that were preferentially re-activated, thus hinting at a stable representation of an

artificially reactivated fear memory [7–9]. Light-induced activation of a fear memory 15 days after fear conditioning preferentially reactivated neuronal populations within the hippocampus, while the same treatment at 90 days preferentially reactivated neuronal populations across various cortical areas, consistent with the notion that the age of a memory differentially recruits neuronal circuits that are modulated by the passage of time. The conceptual advances that these data provide are twofold: they provide evidence that stimulating hippocampus cells processing infantile fear memories is sufficient to drive both the neuronal and behavioral expression fear in adulthood; and they indicate that the hippocampus acts not just as a librarian but as a conductor, capable of coordinating the symphonic cortical–hippocampus medley comprising memory [7,8].

But how do artificial perturbations of the brain yield behaviorally meaningful responses, and how do these responses compare to a natural behavioral response such as memory recall [5,7,10,11]? For example, in adult mice natural freezing levels can reach as high as 80% whereas light-induced freezing tends to hover in the 15–30% range, consistent with the data reported by Guskjolen *et al.* [3] These differences in freezing can be interpreted several ways: perhaps light-induced retrieval of a memory appears weaker because the original memory was not encoded as strongly. Another possibility is that a given memory appears to be distributed in a brain-wide manner, whereas most recent studies tag and manipulate a fraction of cells in a subregion of the brain, which may be insufficient to drive freezing levels to the same magnitude as natural fear memory recall. Or, perhaps a competition with natural sensory cues in a neutral environment mitigates the overall levels of light-induced freezing. Indeed, when light-induced stimulation was paused in experiments of Guskjolen *et al.* [3], the memory seemed to revert back to dormancy, suggesting that natural cues in the environment are not enough for successful memory retrieval even after a memory has been optogenetically jump started, consistent with recent findings [5,7,10,11]. Fittingly, Guskjolen *et al.* [3] provide exciting evidence that a domino effect exists in the brain: whereas an exogenous cue can elicit natural memory retrieval in a given environment, stimulating hippocampus cells processing a discrete memory from within the brain can act as an internal cue to knock over a key node of a domino and elicit the chain reaction of memory retrieval.

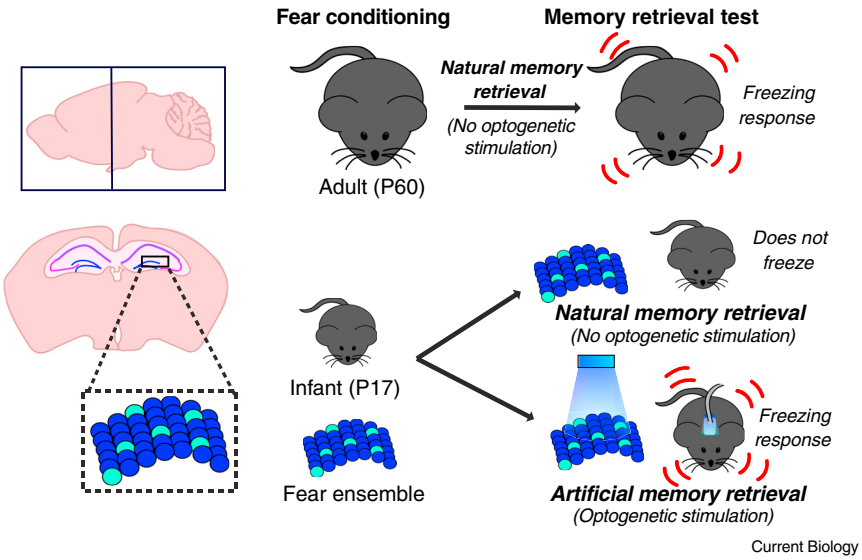

Figure 1. Reawakening a dormant memory trace.
Guskjolen *et al.* [3] first tagged active cells in the dentate gyrus of the hippocampus (left) with light-sensitive opsins. Typically, when an adult mouse (P60) is fear conditioned with a foot shock (indicated by yellow lightning bolt), it will exhibit freezing (indicated by the red lines around the mouse) when reintroduced to the same environment. But if fear conditioning is performed during infancy (P17) and the mouse is subsequently tested during adulthood (P60), the mouse will exhibit amnesia for the fear memory and thus will not freeze. Guskjolen *et al.* [3] were able to reverse this phenomenon in adulthood by optogenetically stimulating the cells that were originally active during fear conditioning in infancy, effectively rescuing the fear memory. A cross-sectional cartoon of the brain (left) indicates what region of the hippocampus was targeted for cellular tagging and stimulation.

Guskjolen *et al.* [3]'s findings also dovetail with previous data from the same group, which builds an experimental scaffold for dissecting the neural mechanisms underlying the developing brain and amnesia. For instance, the group's previous groundbreaking work [12] illustrates the important role that the production of new brain cells, or neurogenesis, plays in infantile amnesia. They reported that high levels of neurogenesis during infancy remodels hippocampal circuitry and leads to impaired memory consolidation and retrieval. Artificially increasing neurogenesis in rodents accelerated their rate of forgetting, while blocking neurogenesis slowed the rate of forgetting, supporting the compelling idea that the rapidly changing nature of a developing brain affects the temporal boundaries of amnesia, and Guskjolen *et al.* [3] show that this boundary can be circumvented when memory-processing hippocampus cells are directly brought back online. The brain sometimes can't remember to forget.

Taken together, Guskjolen *et al.* [3] have directly tapped into the physical manifestation of memory, of an engram, to wake up an infantile memory in adulthood. When Richard Semon coined the term 'engram', he argued for a dynamic perspective of memory processes. Engrams are representations which exist in a latent form in the space between encoding and retrieval. Memory itself is then thought to emerge from the interaction between stored patterns and retrieval cues during the process of recollection [13]. The findings in Guskjolen *et al.* [3] open up experimental floodgates and now enable researchers to ask the following questions related to engrams: what are the physiological and structural properties of engram-bearing cells as they are recruited in infancy and evolve over time into adulthood? How does their activity change in real-time as a memory is pulled out of amnesia? Is there a structural or physiological signature of which cells are susceptible to amnesia? What decides

which memories are forgotten or stored permanently?

Notably, the temporal dynamics inherent to processing memory perhaps pose the next hurdle to be overcome by researchers using strategies capable of artificially activating engrams in the brain with the goals of understanding how to decode memory and how to mimic its physiological structure [14–16]. Optogenetic, chemogenetic, and pharmacological modulation of a circuit cannot yet fully recapitulate the endogenous firing patterns of the brain that occur during learning to drive recall, or test if the former is truly necessary for the latter. The spatial-temporal firing patterns surrounding memory suggest that population codes, time stamps of neural activity, natural drift, and sequences all play a pivotal role in producing the mnemonic pillars that support an engram [14–16]. These are built one fundamental discovery at a time, and Guskjolen *et al.* [3] have provided a promising 21st century window into the mental library we call memory.

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Domestication Genomics: Untangling the Complex History of African Rice

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Study of domestication is complex but essential to our understanding of evolutionary processes and for crop breeding. A new study analyzes genomic data from 163 lines of domesticated African rice and 83 lines of its wild relative, clarifying the history of African rice domestication.

The genomic era offers opportunities to address questions previously difficult to answer. For instance, understanding the process of domestication is crucial to modern agriculture because it illuminates the genetic mechanisms controlling important traits, their evolution, and the basis for their potential improvement through modern breeding efforts. Yet studying domestication can be challenging for a number of reasons: for many crops this process occurred thousands of years in the past and we may lack key data, for example about geographic origins or extinct progenitor populations, and crop demographies are complicated, for example by strong population structure or post-domestication gene flow. All of these factors can cloud a crop's genetic history. The availability of genomic data combined